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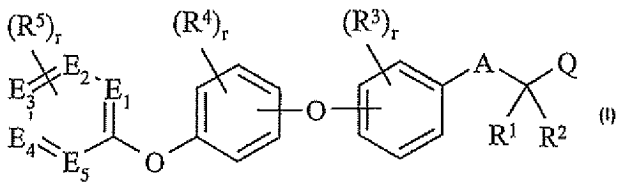
(54) Title: PHENOXYETHER DERIVATIVES AS PPAR MODULATORS



(I)

(57) Abstract: The present invention is directed to a compound of formula (I), or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, which is useful in treating or preventing disorders mediated by a peroxisome proliferator activated receptor (PPAR), such as syndrome X, type II diabetes, hyperglycemia, hyperlipidemia, obesity, coagaulopathy, hypertension, arteriosclerosis, and other disorders related to syndrome X and cardiovascular diseases.

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

PHENOXYETHER DERIVATIVES AS PPAR MODULATORS

FIELD OF THE INVENTION

The present invention relates to compounds of peroxisome proliferator activated receptor (PPAR) agonists, more specifically phenoxyether derivatives as PPAR modulators, which are useful for the treatment and/or prevention of disorders modulated by a PPAR agonist.

BACKGROUND OF THE INVENTION

The peroxisome proliferator activated receptors (PPARs) are members of the nuclear receptor gene family that are activated by fatty acids and fatty acid metabolites. The PPARs belong to the subset of nuclear receptors that function as heterodimers with the 9-*cis* retinoic acid receptor (RXR). Three subtypes, designated PPARα, PPARγ and PPARδ, are found in species ranging from *Xenopus* to humans.

PPARα is the main subtype in the liver and has facilitated analysis of the mechanism by which peroxisome proliferators exert their pleiotropic effects. PPARα is activated by a number of medium and long-chain fatty acids, and it is involved in stimulating β-oxidation of fatty acids. PPARα is also involved with the activity of fibrates and fatty acids in rodents and humans. Fibric acid derivatives such as clofibrate, fenofibrate, bezafibrate, ciprofibrate, beclofibrate and etofibrate, as well as gemfibrozil, produce a substantial reduction in plasma triglycerides along with moderate reduction in low-density lipoprotein (LDL) cholesterol, and they are used particularly for the treatment of hypertriglyceridemia.

PPARγ is the main subtype in adipose tissue and involved in activating the program of adipocyte differentiation. PPARγ is not involved in stimulating peroxisome proliferation in the liver. There are two isomers of PPARγ: PPARγ1 and PPARγ2, which differ only in that PPARγ2 contains an additional 28 amino acids present at the amino terminus. The DNA sequences for the PPARγ receptors are described in Elbrecht, et al., BBRC 224;431-437 (1996). Although peroxisome proliferators, including the fibrates and fatty acids, activate the transcriptional activity of PPAR's, only prostaglandin J_2 derivatives have been identified as natural ligands for PPARγ, which also binds the anti-

diabetic agents thiazolidinediones with high affinity. The physiological functions of PPARα and PPARγ in lipid and carbohydrate metabolism were uncovered once it was recognized that they were the receptors for the fibrate and glitazone drugs, respectively.

PPARα and PPARγ receptors have been implicated in diabetes mellitus, cardiovascular disease, obesity, and gastrointestinal disease, such as inflammatory bowel disease and other inflammation related illnesses. Such inflammation related illnesses include, but are not limited to Alzheimer's disease, Crohn's disease, rheumatoid arthritis, psoriasis, and ischemia reprofusion injury.

By contrast, PPARδ (also referred to as PPARβ and NUC1) is not reported to be receptor for any known class of drug molecules, and its role in mammalian physiology has remained undefined. The human nuclear receptor gene PPARδ (hPPARδ) has been cloned from a human osteosarcoma cell cDNA library and is fully described in A. Schmidt et al., *Molecular Endocrinology*, 6:1634-1641 (1992).

Diabetes is a disease in which a mammal's ability to regulate glucose levels in the blood is impaired because the mammal has a reduced ability to convert glucose to glycogen for storage in muscle and liver cells. In Type I diabetes, this reduced ability to store glucose is caused by reduced insulin production. "Type II Diabetes" or "non-insulin dependent diabetes mellitus" (NIDDM) is the form of diabetes, which is due to a profound resistance to insulin stimulating or regulatory effect on glucose and lipid metabolism in the main insulin-sensitive tissues, muscle, liver and adipose tissue. This resistance to insulin responsiveness results in insufficient insulin activation of glucose uptake, oxidation and storage in muscle and inadequate insulin repression of lipolysis in adipose tissue and of glucose production and secretion in liver. When these cells become desensitized to insulin, the body tries to compensate by producing abnormally high levels of insulin and hyperinsulemia results. Hyperinsulemia is associated with hypertension and elevated body weight. Since insulin is involved in promoting the cellular uptake of glucose, amino acids and triglycerides from the blood by insulin sensitive cells, insulin insensitivity can result in elevated levels of triglycerides and LDL (known as the "bad" cholesterol) which are risk factors in cardiovascular diseases. The constellation of symptoms, which includes hyperinsulemia, combined with hypertension, elevated body weight, elevated triglycerides and elevated LDL is known as Syndrome X.

Hyperlipidemia is a condition, which is characterized by an abnormal increase in serum lipids, such as cholesterol, triglycerides and phospholipids. These lipids do not circulate freely in solution in plasma, but are bound to proteins and transported as macromolecular complexes called lipoproteins. One form of hyperlipidemia is hypercholesterolemia, characterized by the existence of elevated LDL cholesterol levels. The initial treatment for hypercholesterolemia is often a diet low in fat and cholesterol coupled with appropriate physical exercise. Drug intervention is initiated if LDL-lowering goals are not met by diet and exercise alone. It is desirable to lower elevated levels of LDL cholesterol and increase levels of HDL cholesterol. Generally, it has been found that increased levels of HDL are associated with lower risk for coronary heart disease (CHD). See Gordon, et al., *Am. J. Med.*, 62, 707-714 (1977); Stampfer, et al., *N. England J. Med.*, 325, 373- 381 (1991); and Kannel, et al., *Ann. Internal Med.*, 90, 85-91 (1979). An example of an HDL raising agent is nicotinic acid, but the quantities needed to achieve HDL elevation are associated with undesirable effects, such as flushing.

There are several treatments currently available for treating diabetes mellitus but these treatments still remain unsatisfactory and have limitations. While physical exercise and reduction in dietary intake of calories will improve the diabetic condition, compliance with this approach can be poor because of sedentary lifestyles and excess food consumption, in particular high fat-containing food. Therefore, treatment with hypoglycemics, such as sulfonylureas (e.g., chlorpropamide, tolbutamide, tolazamide and acetohexamide) and biguanides (e.g. phenformin and metformin) are often necessary as the disease progresses. Sulfonylureas stimulate the β cells of the pancreas to secrete more insulin as the disease progresses. However, the response of the β cells eventually fails and treatment with insulin injections is necessary. In addition, both sulfonylurea treatment and insulin injection have the life threatening side effect of hypoglycemic coma, and thus patients using these treatments must carefully control dosage.

It has been well established that improved glycemic control in patients with diabetes (Type I and Type II) is accompanied by decreased microvasclular complications (DCCT and UKPDS). Due to difficulty in maintaining adequate glycemic control over time in patients with Type II diabetes, the use of insulin sensitizers in the therapy of Type II diabetes is growing. There is also a growing body of evidence that

PPARγ agonist, insulin sensitizer, may have benefits in the treatment of Type II diabetes beyond their effects in improving glycemic control.

In the last decade a class of compounds known as thiazolidinediones (TZD) (e.g. U.S. Pat. Nos. 5,089,514; 4,342,771; 4,367,234; 4,340,605; and 5,306,726) have emerged as effective antidiabetic agents that have been shown to increase the sensitivity of insulin sensitive tissues, such as skeletal muscle, liver and adipose, to insulin. Increasing insulin sensitivity rather than the amount of insulin in the blood reduces the likelihood of hypoglycemic coma. Although thiazolidinediones have been shown to increase insulin sensitivity by binding to PPARγ receptors, this treatment also produces unwanted side effects such as weight gain and, for troglitazone, liver toxicity.

Recently, compounds that are not TZDs have also been reported.

Adams et al. (WO 97/28115, WO 97/28135 and US Patent No. 5,895,051) discloses acetylphenols, which are useful as antiobesity and antidiabetic compounds.

Leibowitz et al. (WO 97/28149) discloses compounds which are PPARδ agonists and useful for treating cardiovascular diseases and related conditions.

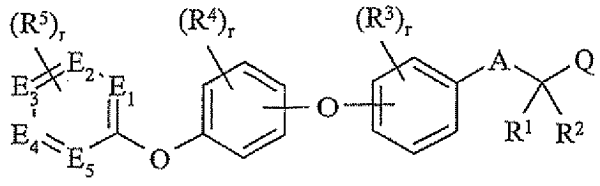
Brooks et al. (WO 02/100813) discloses compounds of PPAR modulators that are useful for treating type II diabetes and other PPAR-mediated diseases and conditions.

In view of the above, an objective of the present invention is to provide new pharmaceutical agents, which modulate PPAR receptors, to prevent, treat and/or alleviate these diseases or conditions while reducing and or eliminating one or more of the unwanted side effects associated with the current treatments.

SUMMARY OF THE INVENTION

The present invention relates to a compound of novel peroxisome proliferator activated receptor (PPAR) agonist having a structural formula I,

A compound having a formula I,



I

or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein: E_1, E_2, E_3, E_4 and E_5 are each CH or substituted carbon bearing R^5; or at least one of E_1, E_2, E_3, E_4 and E_5 is nitrogen and each of others being CH or substituted carbon bearing R^5;

A is: a bond, CH_2, $(CH_2)_2$, O, S; or A and R^1 or A and R^2 together being a 3- to 6-membered carbocyclyl when A is a carbon;

Q is: $-C(O)OR^6$ or R^{6A};

n is: 1, 2, 3, 4, 5 or 6

p is: 1 or 2;

r is: 1, 2, 3, or 4;

R^1 and R^2 are each independently:

hydrogen, C_1-C_6 alkyl, or R^1 and R^2 together being a 3- to 8-membered carbocyclic ring;

R^3 and R^4 are each independently:

hydrogen,
nitro,
cyano,
hydroxyl,
halo,
haloalkyl,
haloalkyloxy,
C_1-C_6 alkyl,
C_1-C_6 alkoxy, or
C_3-C_8 cycloalkyl

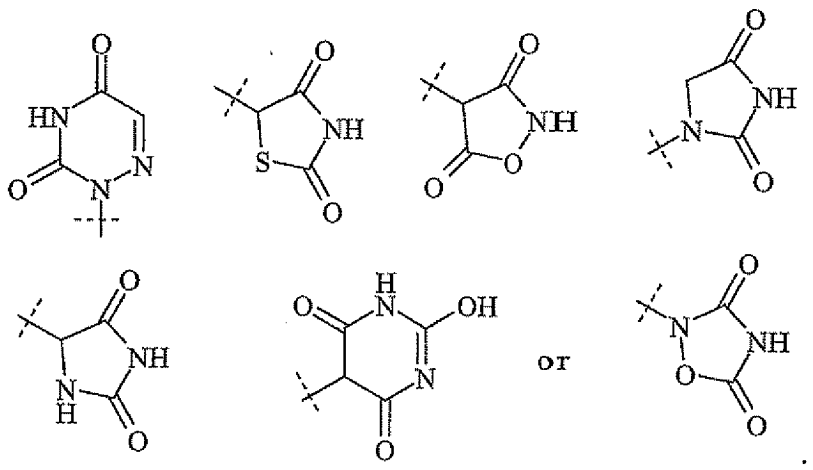
R^5 is: hydrogen,
nitro,

cyano,
hydroxyl,
halo,
haloalkyl,
haloalkyloxy,
aryloxy,
C_1-C_6 alkyl,
C_1-C_6 alkoxy,
[T]-aryl,
[T]-heteroaryl,
[T]-heterocyclyl,
[T]-$(CH_2)_nC_3$-C_8 cycloalkyl,
$C(O)_pR^7$,
$O(CH_2)_nR^7$,
SR^7,
$S(O)_pR^7$ or
$OS(O)_pR^7$,
wherein aryl, aryloxy, alkyl, heteroaryl, heterocyclyl and cycloalkyl are being optionally substituted with one or more substituents independently selected from R^8;

[T] is: a bond, O, C(O), S, NR^7, or C_1-C_6 alkyl;

R^6 is: hydrogen, C_1-C_6 alkyl or aminoalkyl;

R^{6A} is: carboxamide, sulfonamide, acylsulfonamide, tetrazole,



;

R^7 is: hydrogen,
C_1-C_6 alkyl,
C_3-C_8 cycloalkyl,
aryl,
heteroaryl or
heterocyclyl,
wherein alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl being optionally substituted with one or more substituents independently selected from R^8; and

R^8 is: hydrogen, nitro, cyano, hydroxyl, halo, haloalkyl, haloalkyloxy, aryloxy, oxo, acyl, C_1-C_6 alkyl, C_1-C_6 alkoxy or C_3-C_8 cycloalkyl.

The compounds of the present invention are useful in the treatment and/or prevention of diseases or condition relates to hyperglycemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity, anorexia bulimia, anorexia nervosa, cardiovascular disease and other diseases where insulin resistance is a component.

In one embodiment, the present invention also relates to a pharmaceutical composition comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate or hydrate thereof and a pharmaceutically acceptable carrier. Within the scope of this invention also include a pharmaceutical composition containing

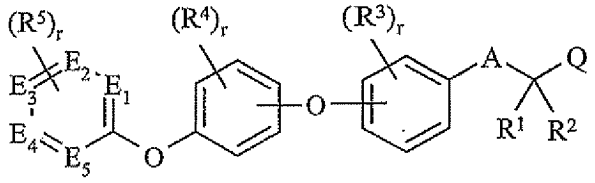
additional therapeutic agent as well as a compound of the present invention, or a pharmaceutically acceptable salt, solvate or hydrate thereof and a pharmaceutically acceptable carrier.

In another embodiment, the present invention relates to a method of modulating a PPAR by contacting the receptor with a compound of the present invention, and a pharmaceutically acceptable salt, solvate or hydrate thereof.

DETAILED DESCRIPTION OF THE INVENTION

The compounds of the present invention are directed to peroxisome proliferator activated receptor (PPAR) agonists, more specifically phenoxyether derivatives as PPAR modulators. The compounds of the present invention are directed to PPAR-γ/δ dual agonists. The compounds of the present invention are useful for the treatment and/or prevention of disorders modulated by a PPAR, such as Type II diabetes, hyperglycemia, dyslipidemia, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity, anorexia bulimia, anorexia nervosa, cardiovascular disease and other related diseases.

An embodiment of the present invention is a compound of novel peroxisome proliferator activated receptor (PPAR) agonists having a structural formula I,



I

or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein: E_1, E_2, E_3, E_4 and E_5 are each CH or substituted carbon bearing R^5; or at least one of E_1, E_2, E_3, E_4 and E_5 is nitrogen and each of others being CH or substituted carbon bearing R^5;

A is: a bond, CH_2, $(CH_2)_2$, O, S; or A and R^1 or A and R^2 together being a 3- to 6-membered carbocyclyl when A is a carbon;

Q is: $-C(O)OR^6$ or R^{6A};

n is: 1, 2, 3, 4, 5 or 6

p is: 1 or 2;

r is: 1, 2, 3, or 4;

R^1 and R^2 are each independently:

hydrogen, C_1-C_6 alkyl, or R^1 and R^2 together being a 3- to 8-membered carbocyclic ring;

R^3 and R^4 are each independently:

hydrogen,
nitro,
cyano,
hydroxyl,
halo,
haloalkyl,
haloalkyloxy,
C_1-C_6 alkyl,
C_1-C_6 alkoxy, or
C_3-C_8 cycloalkyl

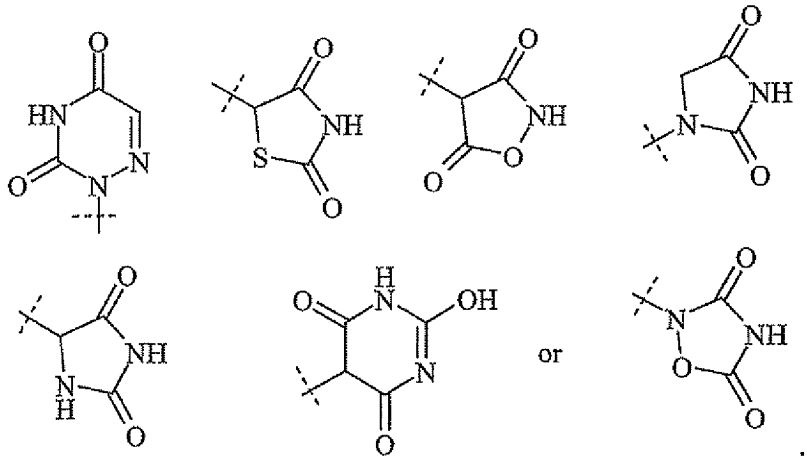
R^5 is: hydrogen,
nitro,
cyano,
hydroxyl,
halo,
haloalkyl,
haloalkyloxy,
aryloxy,
C_1-C_6 alkyl,
C_1-C_6 alkoxy,
[T]-aryl,

[T]-heteroaryl,
[T]-heterocyclyl,
[T]-$(CH_2)_nC_3$-C_8 cycloalkyl,
$C(O)_pR^7$,
$O(CH_2)_nR^7$,
SR^7,
$S(O)_pR^7$ or
$OS(O)_pR^7$,
wherein aryl, aryloxy, alkyl, heteroaryl, heterocyclyl and cycloalkyl are being optionally substituted with one or more substituents independently selected from R^8;

[T] is: a bond, O, C(O), S, NR^7, or C_1-C_6 alkyl;

R^6 is: hydrogen, C_1-C_6 alkyl or aminoalkyl;

R^{6A} is: carboxamide, sulfonamide, acylsulfonamide, tetrazole,



;

R^7 is: hydrogen,
C_1-C_6 alkyl,
C_3-C_8 cycloalkyl,
aryl,

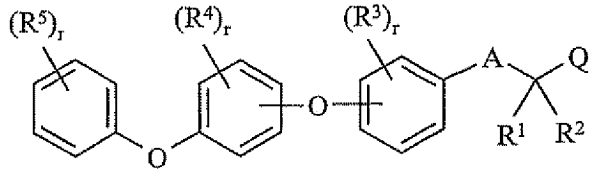
heteroaryl or

heterocyclyl,

wherein alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl being optionally substituted with one or more substituents independently selected from R^8; and

R^8 is: hydrogen, nitro, cyano, hydroxyl, halo, haloalkyl, haloalkyloxy, aryloxy, oxo, acyl, C_1-C_6 alkyl, C_1-C_6 alkoxy or C_3-C_8 cycloalkyl.

A preferred embodiment of the present invention is a compound having a structural formula II,



II

or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein:

A is: a bond, CH_2, $(CH_2)_2$, O, S; or A and R^1 or A and R^2 together being a 3- to 6-membered carbocyclyl when A is a carbon;

Q is: $-C(O)OR^6$ or R^{6A};

n is: 1, 2, 3, 4, 5 or 6

p is: 1 or 2;

r is: 1, 2, 3, or 4;

R^1 and R^2 are each independently:

hydrogen, C_1-C_6 alkyl, or R^1 and R^2 together being a 3- to 8-membered carbocyclic ring;

R^3 and R^4 are each independently:

hydrogen,

nitro,

cyano,

hydroxyl,

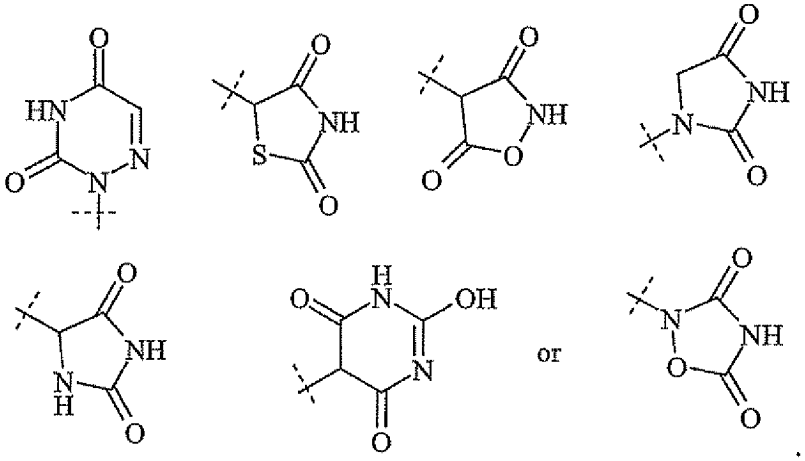
halo,
haloalkyl,
haloalkyloxy,
C_1-C_6 alkyl,
C_1-C_6 alkoxy, or
C_3-C_8 cycloalkyl;

R^5 is: hydrogen,
nitro,
cyano,
hydroxyl,
halo,
haloalkyl,
haloalkyloxy,
aryloxy,
C_1-C_6 alkyl,
C_1-C_6 alkoxy,
[T]-aryl,
[T]-heteroaryl,
[T]-heterocyclyl,
[T]-$(CH_2)_nC_3$-C_8 cycloalkyl,
$C(O)_pR^7$,
$O(CH_2)_nR^7$,
SR^7,
$S(O)_pR^7$ or
$OS(O)_pR^7$,
wherein aryl, aryloxy, alkyl, heteroaryl, heterocyclyl and cycloalkyl are being optionally substituted with one or more substituents independently selected from R^8;

[T] is: a bond, O, C(O), S, NR^7, or C_1-C_6 alkyl;

R^6 is: hydrogen, C_1-C_6 alkyl or aminoalkyl;

R^{6A} is: carboxamide, sulfonamide, acylsulfonamide, tetrazole,



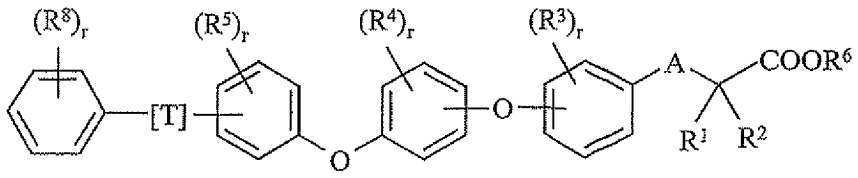
or

;

R^7 is: hydrogen,
C_1-C_6 alkyl,
C_3-C_8 cycloalkyl,
aryl,
heteroaryl or
heterocyclyl,
wherein alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl being optionally substituted with one or more substituents independently selected from R^8; and

R^8 is: hydrogen, nitro, cyano, hydroxyl, halo, haloalkyl, haloalkyloxy, aryloxy, oxo, acyl, C_1-C_6 alkyl, C_1-C_6 alkoxy or C_3-C_8 cycloalkyl.

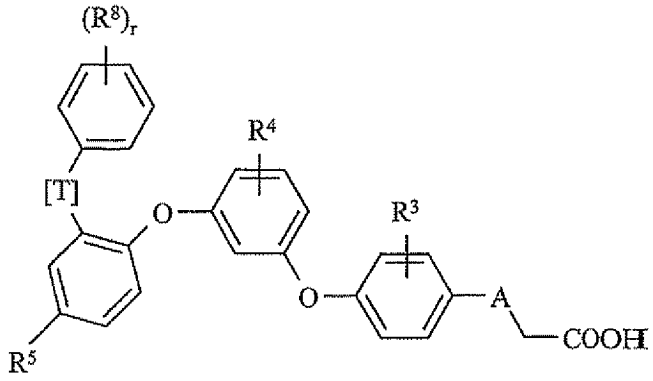
Another preferred embodiment of the present invention is a compound having a structural formula III,



III

or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof.

Yet another preferred embodiment of the present invention is the compound having a structural formula IV,



IV

or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein:

A is: CH_2, O, S;

[T] is: a bond, O, C(O) or C_1-C_3 alkyl;

R^3 and R^4 are each independently:

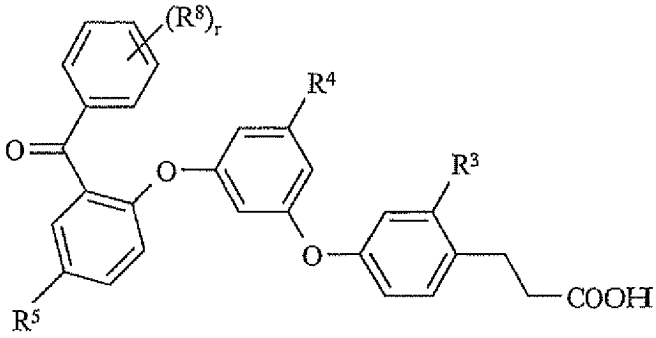
hydrogen, C_1-C_3 alkyl, halo, haloalkyl or haloalkyloxy;

R^5 and R^8 are each independently:

hydrogen, C_1-C_6 alkyl, halo, haloalkyl or haloalkyloxy; and

r is 1 or 2.

Yet another preferred embodiment of the present invention is the compound having a structural formula V,



V

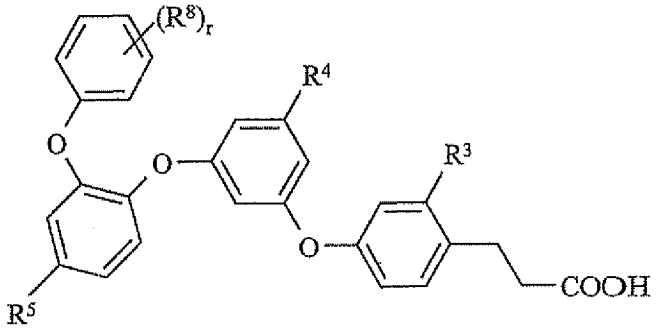
or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein:

R^3 and R^4 are each independently: hydrogen, methyl, ethyl, Br, Cl or F;

R^5 and R^8 are each independently: hydrogen, C_1-C_4 alkyl, Br, Cl, F or CF_3; and

r is 1 or 2.

Yet another embodiment of the present invention is a compound having a structural formula VI,



VI

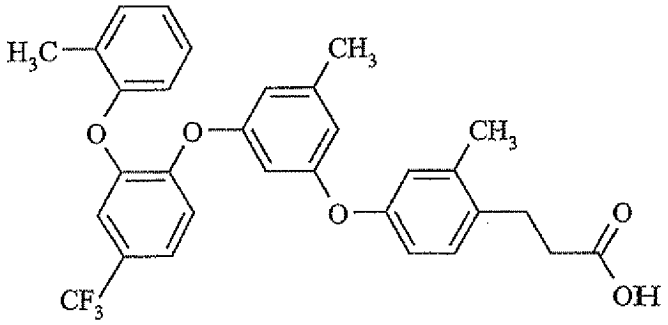
or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein:

R^3 and R^4 are each independently: hydrogen, methyl, ethyl, Br, Cl or F;

R^5 and R^8 are each independently: hydrogen, C_1-C_4 alkyl, Br, Cl, F or CF_3; and

r is 1 or 2.

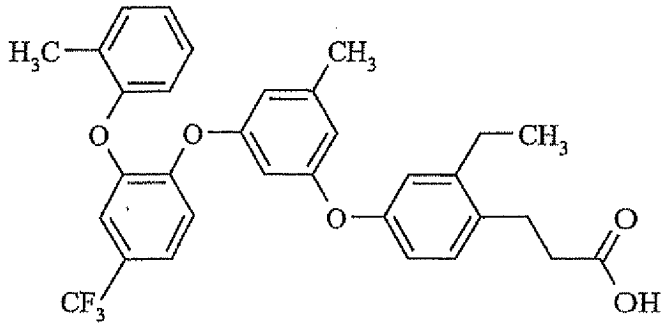
Yet another preferred embodiment of the present invention is the compound having a structural formula VII,



VII

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

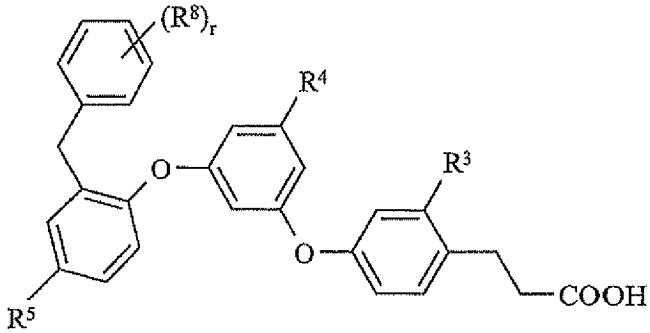
Yet another preferred embodiment of the present invention is the compound having a structural formula VIII,



VIII

or a pharmaceutically acceptable salt, solvate or hydrate thereof.

Yet another preferred embodiment of the present invention is a compound having a structural formula IX,



IX

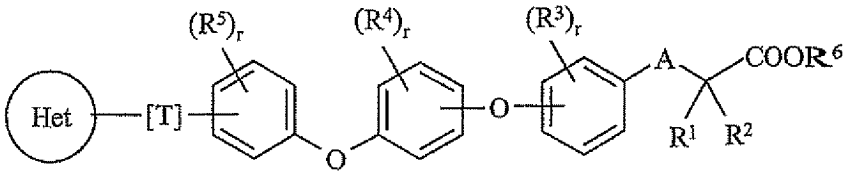
or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein:

R^3 and R^4 are each independently: hydrogen, methyl, ethyl, Br, Cl or F;

R^5 and R^8 are each independently: hydrogen, C_1-C_4 alkyl, Br, Cl, F or CF_3; and

r is 1 or 2.

Yet another preferred embodiment of the present invention is a compound having a structural formula X,



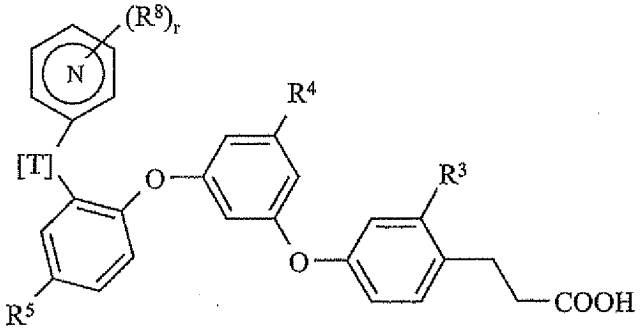
X

or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein:

Het is a 5- or 6-membered heteroaryl or heterocyclyl, wherein heteroaryl and heterocyclyl being optionally substituted with one or more substituents independently selected from R^8.

The compound as recited above in formula X, wherein the heteroaryl is pyrazolyl, pyrrolyl, pyrazinyl, pyridyl, pyrimidyl or pyrimidinyl

Yet another preferred embodiment of the present invention is a compound having a structural formula XI,



XI

or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein:

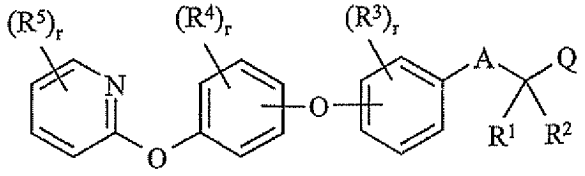
[T] is: a bond, O, C(O) or C_1-C_3 alkyl;

R^3 and R^4 are each independently: hydrogen, methyl, ethyl, Br, Cl or F;

R^5 and R^8 are each independently: hydrogen, C_1-C_4 alkyl, Br, Cl, F or CF_3; and

r is 1 or 2.

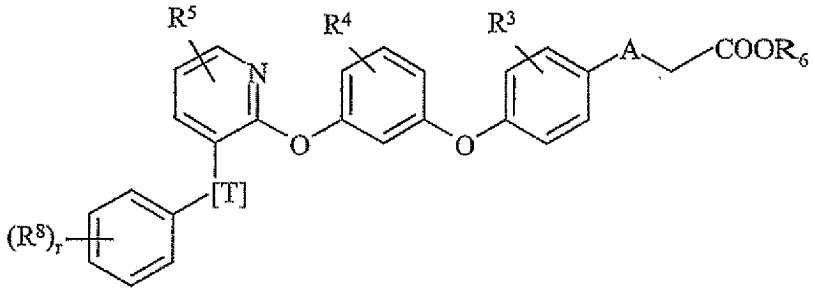
Yet another preferred embodiment of the present invention is a compound having a structural formula XII,



XII

or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof.

Yet another preferred embodiment of the present invention is a compound having a structural formula XIII,



XIII

or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein:

A is: CH_2, O, S;

[T] is: a bond, O, C(O) or C_1-C_3 alkyl;

R^3 and R^4 are each independently:

hydrogen, C_1-C_3 alkyl, halo, haloalkyl or haloalkyloxy;

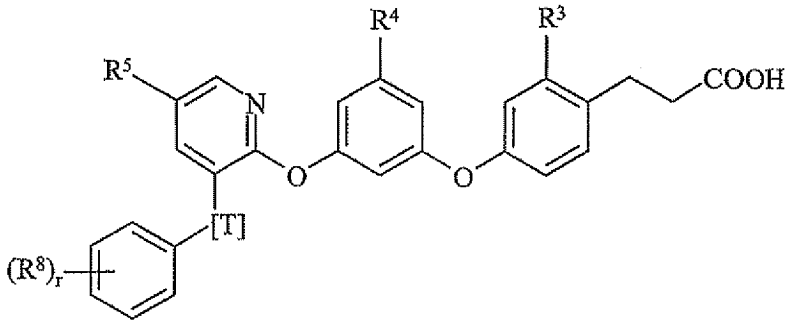
R^5 and R^8 are each independently:

hydrogen, C_1-C_6 alkyl, halo, haloalkyl or haloalkyloxy; and

R^6 is: hydrogen or C_1-C_6 alkyl; and

r is 1 or 2.

Yet another preferred embodiment of the present invention is a compound having a structural formula XIV,



XIV

or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, wherein:

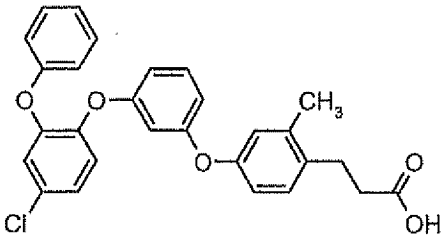
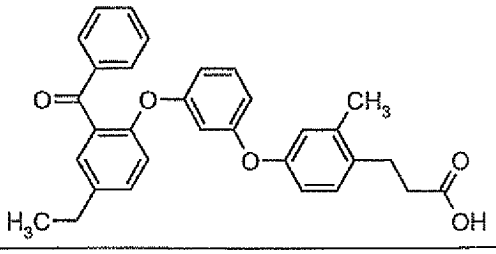
[T] is: a bond, O or C_1-C_3 alkyl;

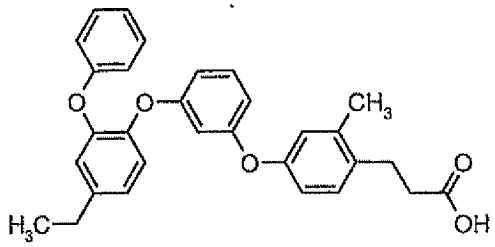
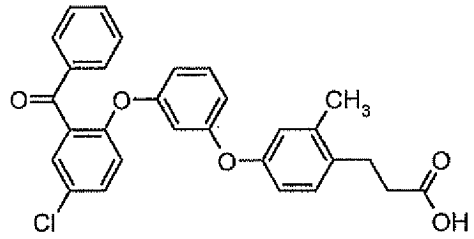
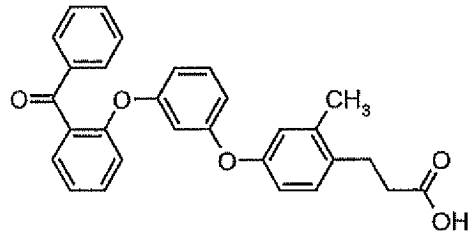
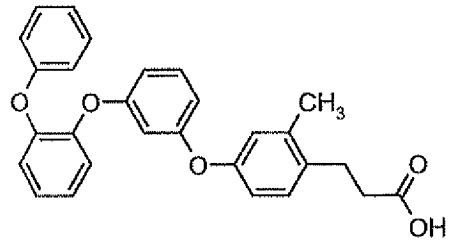
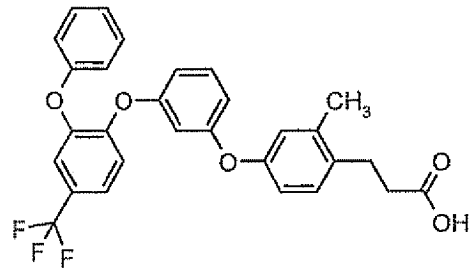
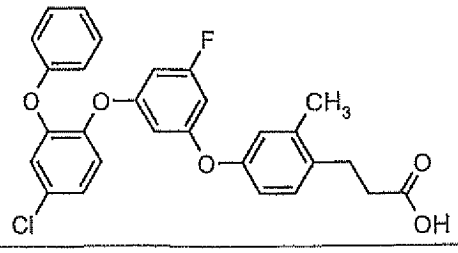
R^3 and R^4 are each independently: hydrogen, methyl, ethyl, Br, Cl or F;

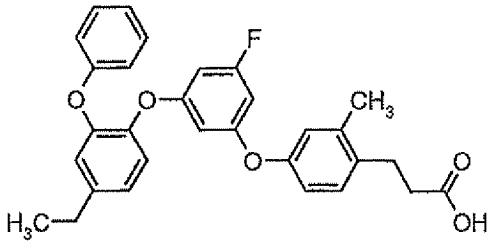
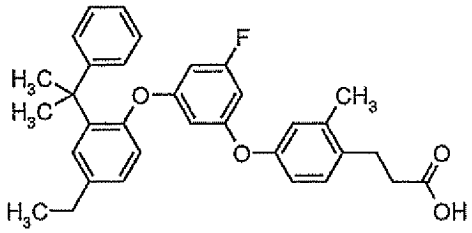
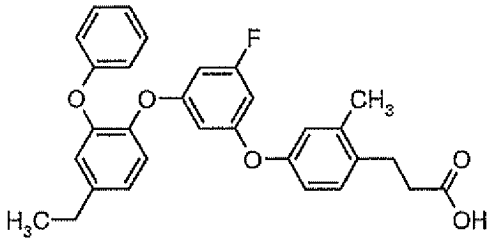
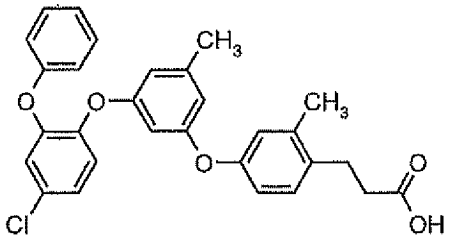
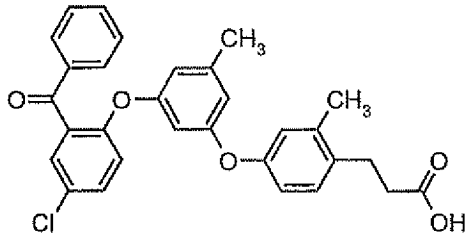
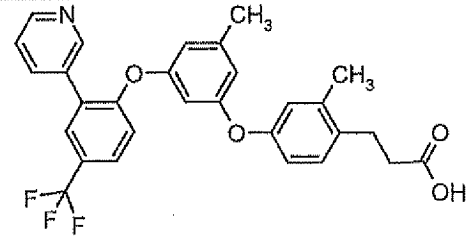
R^5 and R^8 are each independently: hydrogen, C_1-C_4 alkyl, Br, Cl, F or CF_3; and

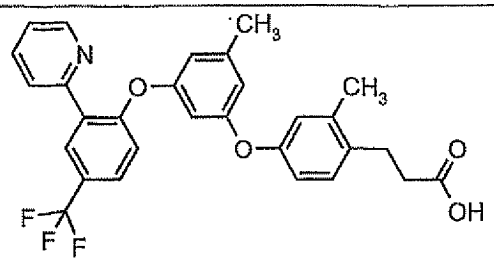
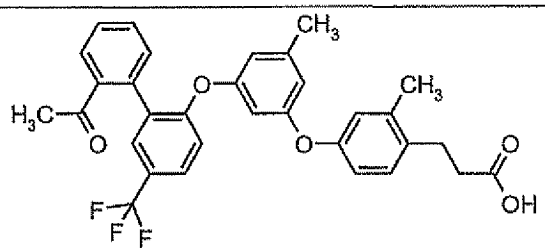
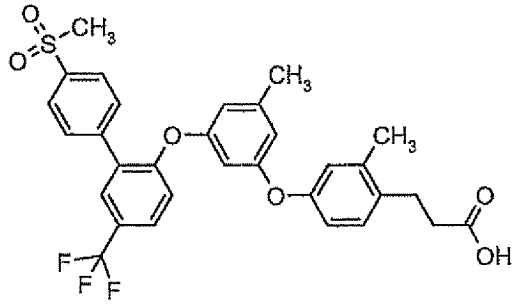
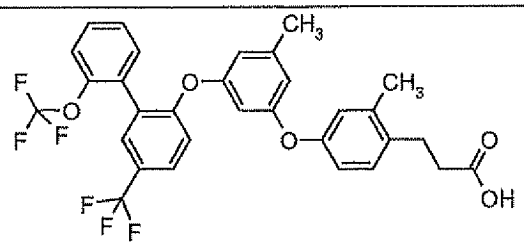
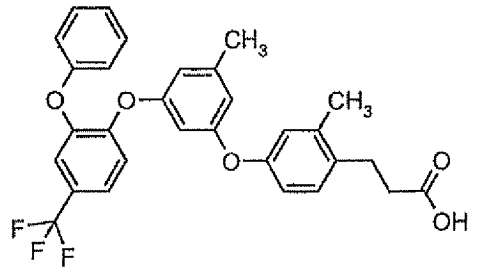
r is 1 or 2.

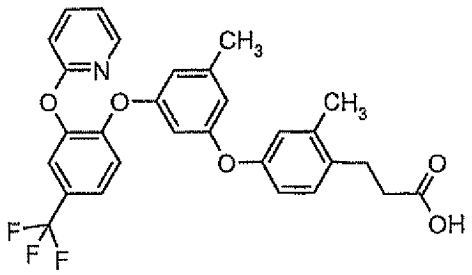
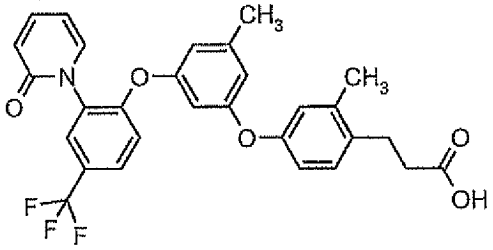
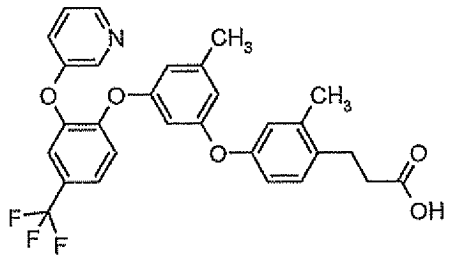
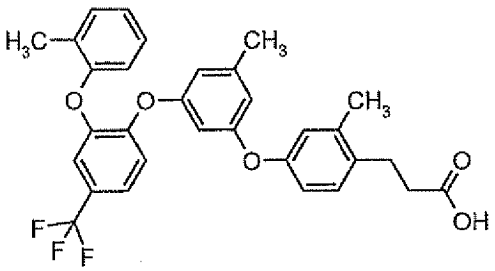
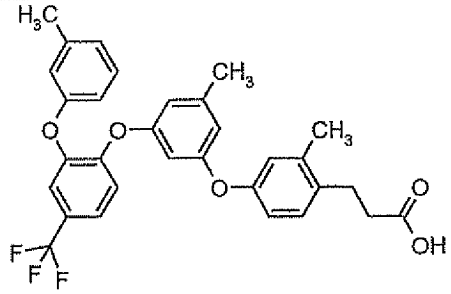
Yet more preferred embodiment of the present invention is the compounds listed below:

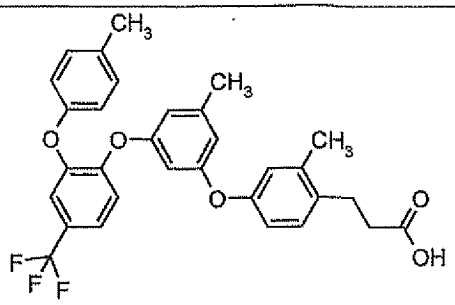
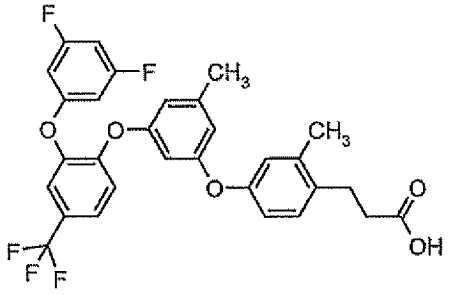
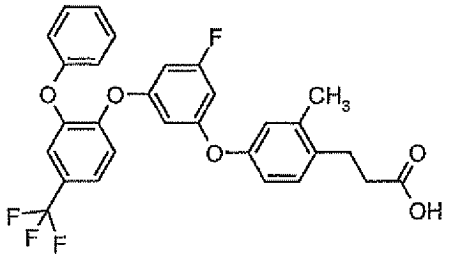
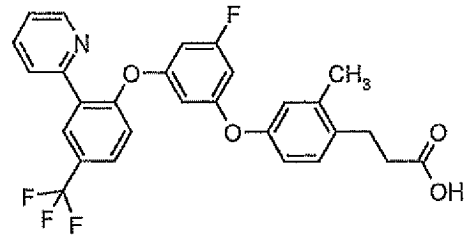
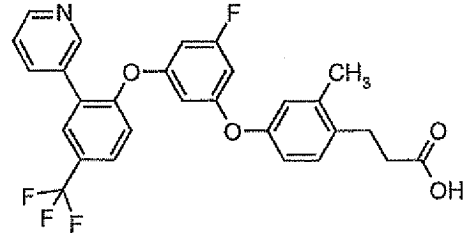
No.	Structure	Name
1		3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid
2		3-{4-[3-(2-Benzoyl-4-ethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid

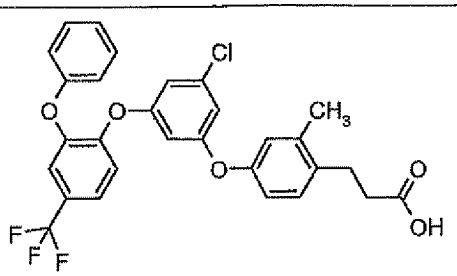
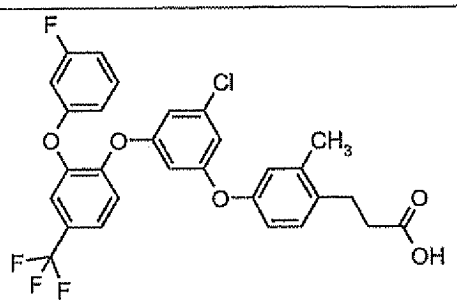
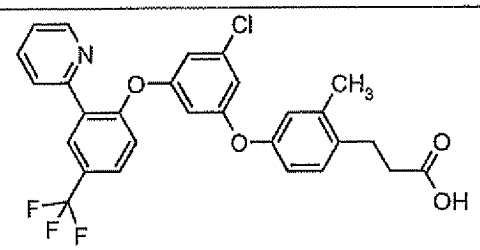
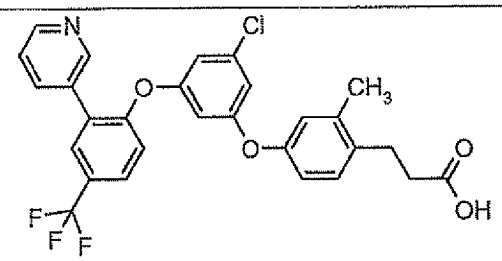
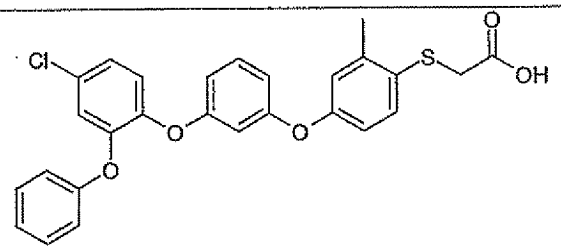
No.	Structure	Name
3		3-{4-[3-(4-Ethyl-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid
4		3-{4-[3-(2-Benzoyl-4-chloro-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid
5		3-{4-[3-(2-Benzoyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid
6		3-{2-Methyl-4-[3-(2-phenoxy-phenoxy)-phenoxy]-phenyl}-propionic acid
7		3-{2-Methyl-4-[3-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid
8		3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid

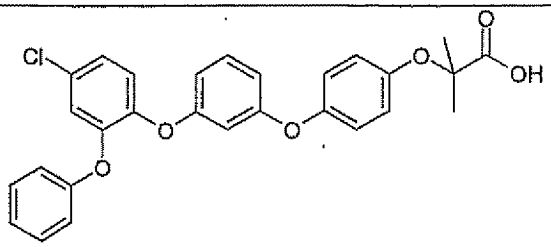
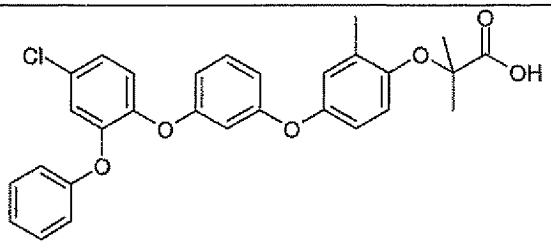
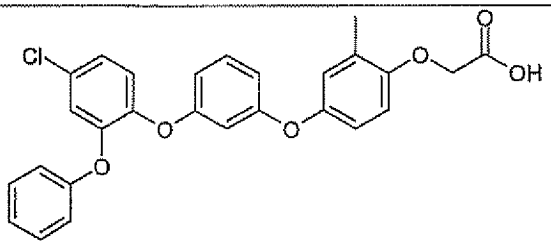
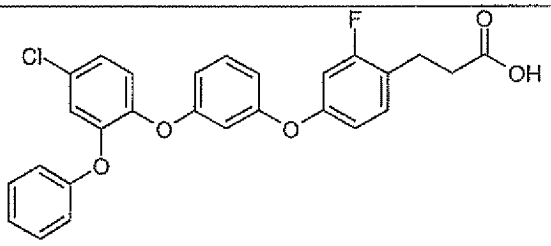
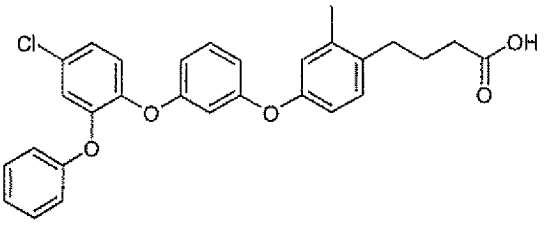
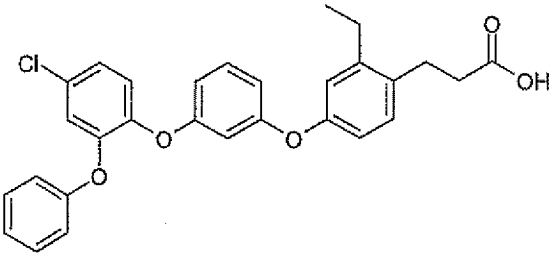
No.	Structure	Name
9		3-{4-[3-(4-Ethyl-2-phenoxy-phenoxy)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid
10		3-(4-{3-[4-Ethyl-2-(1-methyl-1-phenyl-ethyl)-phenoxy]-5-fluoro-phenoxy}-2-methyl-phenyl)-propionic acid
11		3-{4-[3-(4-Ethyl-2-phenoxy-phenoxy)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid
12		3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid
13		3-{4-[3-(2-Benzoyl-4-chloro-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid
14		3-{2-Methyl-4-[3-methyl-5-(2-pyridin-3-yl-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid

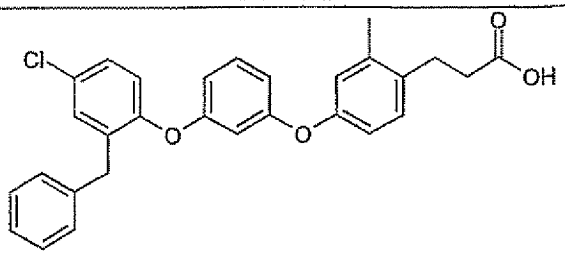
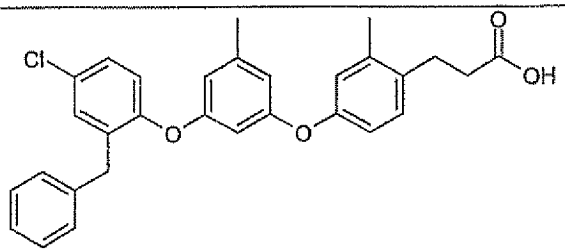
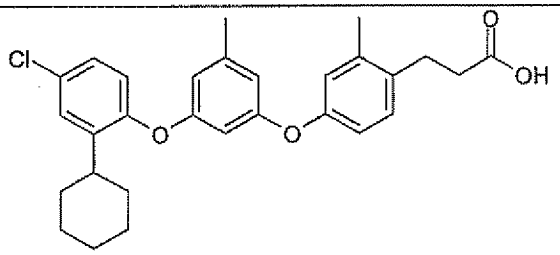
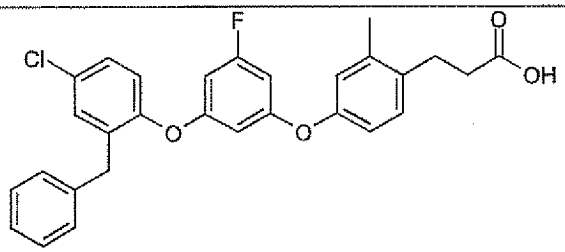
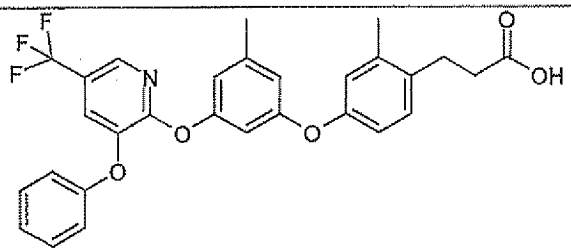
No.	Structure	Name
15		3-{2-Methyl-4-[3-methyl-5-(2-pyridin-2-yl-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid
16		3-{4-[3-(2'-Acetyl-5-trifluoromethyl-biphenyl-2-yloxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid
17		3-{4-[3-(4'-Methanesulfonyl-5-trifluoromethyl-biphenyl-2-yloxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid
18		3-{2-Methyl-4-[3-methyl-5-(2'-trifluoromethoxy-5-trifluoromethyl-biphenyl-2-yloxy)-phenoxy]-phenyl}-propionic acid
19		3-{2-Methyl-4-[3-methyl-5-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid

No.	Structure	Name
20		3-(2-Methyl-4-{3-methyl-5-[2-(pyridin-2-yloxy)-4-trifluoromethyl-phenoxy]-phenoxy}-phenyl)-propionic acid
21		3-(2-Methyl-4-{3-methyl-5-[2-(2-oxo-2H-pyridin-1-yl)-4-trifluoromethyl-phenoxy]-phenoxy}-phenyl)-propionic acid
22		3-(2-Methyl-4-{3-methyl-5-[2-(pyridin-3-yloxy)-4-trifluoromethyl-phenoxy]-phenoxy}-phenyl)-propionic acid
23		3-{2-Methyl-4-[3-methyl-5-(2-o-tolyloxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid
24		3-{2-Methyl-4-[3-methyl-5-(2-m-tolyloxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid

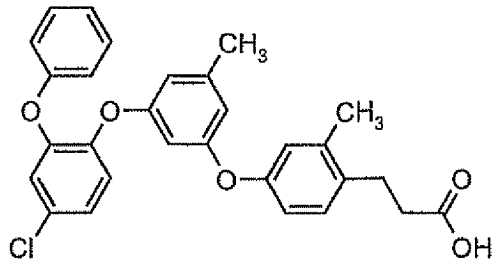
No.	Structure	Name
25		3-{2-Methyl-4-[3-methyl-5-(2-p-tolyloxy-4-trifluoromethyl-phenoxy)-phenoxy]-phenyl}-propionic acid
26		3-(4-{3-[2-(3,5-Difluoro-phenoxy)-4-trifluoromethyl-phenoxy]-5-methyl-phenoxy}-2-methyl-phenyl)-propionic acid
27		3-{4-[3-Fluoro-5-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid
28		3-{4-[3-Fluoro-5-(2-pyridin-2-yl-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid
29		3-{4-[3-Fluoro-5-(2-pyridin-3-yl-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid

No.	Structure	Name
30		3-{4-[3-Chloro-5-(2-phenoxy-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid
31		3-(4-{3-Chloro-5-[2-(3-fluoro-phenoxy)-4-trifluoromethyl-phenoxy]-phenoxy}-2-methyl-phenyl)-propionic acid
32		3-{4-[3-Chloro-5-(2-pyridin-2-yl-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid
33		3-{4-[3-Chloro-5-(2-pyridin-3-yl-4-trifluoromethyl-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid
34		{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenylsulfanyl}-acetic acid

No.	Structure	Name
35		2-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-phenoxy}-2-methyl-propionic acid
36		2-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenoxy}-2-methyl-propionic acid
37		{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenoxy}-acetic acid
38		3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-fluoro-phenyl}-propionic acid
39		4-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenyl}-butyric acid
40		3-{4-[3-(4-Chloro-2-phenoxy-phenoxy)-phenoxy]-2-ethyl-phenyl}-propionic acid

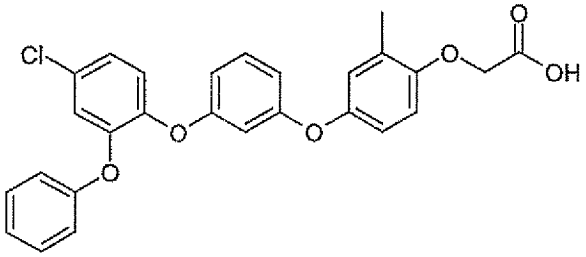
No.	Structure	Name
41		3-{4-[3-(2-Benzyl-4-chloro-phenoxy)-phenoxy]-2-methyl-phenyl}-propionic acid
42		3-{4-[3-(2-Benzyl-4-chloro-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid
43		3-{4-[3-(4-Chloro-2-cyclohexyl-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid
44		3-{4-[3-(2-Benzyl-4-chloro-phenoxy)-5-fluoro-phenoxy]-2-methyl-phenyl}-propionic acid
45		3-{2-Methyl-4-[3-methyl-5-(3-phenoxy-5-trifluoromethyl-pyridin-2-yloxy)-phenoxy]-phenyl}-propionic acid

Yet more preferred embodiment of the present invention is the compounds of 3-{4-[3-(4-chloro-2-phenoxy-phenoxy)-5-methyl-phenoxy]-2-methyl-phenyl}-propionic acid having the following structure,



or a pharmaceutically acceptable salt, solvate or hydrate thereof.

Yet more preferred embodiment of the present invention is the compounds of {4-[3-(4-chloro-2-phenoxy-phenoxy)-phenoxy]-2-methyl-phenoxy}-acetic acid having the following structure,



or a pharmaceutically acceptable salt, solvate or hydrate thereof.

Also encompassed by the present invention is a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound of the present invention or a pharmaceutically acceptable salt, solvate or hydrate thereof.

Also encompassed by the present invention is a pharmaceutical composition comprising: (1) a compound of the present invention, or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof; (2) a second therapeutic agent selected from the group consisting of: insulin sensitizers, sulfonylureas, biguanides, meglitinides, thiazolidinediones, α-glucosidase inhibitors, insulin secretogogues, insulin, antihyperlipidemic agents, plasma HDL-raising agents, HMG-CoA reductase inhibitors, statins, acryl CoA:cholestrol acyltransferase inhibitors, antiobesity compounds, antihypercholesterolemic agents, fibrates, vitamins and aspirin; and (3) optionally a pharmaceutically acceptable carrier.

Also encompassed by the present invention is a method of modulating a peroxisome proliferator activated receptor (PPAR) comprising the step of contacting the receptor with a compound of the present invention or a pharmaceutically acceptable salt, solvate or hydrate thereof.

The method recited above, wherein the PPAR is an alpha (α)-receptor.

The method recited above, wherein the PPAR is a gamma (γ)-receptor.

The method recited above, wherein the PPAR is a delta (δ)-receptor.

The method recited above, wherein the PPAR is a gamma/delta (γ/δ)-receptor.

The method recited above, wherein the PPAR is a alpha/gamma/delta (α/γ/δ)-receptor.

Also encompassed by the present invention is a method for treating and/or preventing a PPAR-γ mediated disease or condition in a mammal comprising the step of administering an effective amount of a compound of the present invention.

Also encompassed by the present invention is a method for treating and/or preventing a PPAR-δ mediated disease or condition in a mammal comprising the step of administering an effective amount of a compound of the present invention.

Also encompassed by the present invention is a method for treating and/or preventing a PPAR-γδ mediated disease or condition in a mammal comprising the step of administering an effective amount of a compound of the present invention.

Also encompassed by the present invention is a method for treating and/or preventing a PPARα/γ/δ-mediated disease or condition in a mammal comprising the step of administering an effective amount of a compound of the present invention.

Also encompassed by the present invention is a method for lowering blood-glucose in a mammal comprising the step of administering an effective amount of a compound of the present invention.

Also encompassed by the present invention is a method of treating and/or preventing disease or condition in a mammal selected from the group consisting of hyperglycemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity, anorexia bulimia, anorexia nervosa,

cardiovascular disease and other diseases where insulin resistance is a component, comprising the step of administering an effective amount of a compound of a compound of the present invention.

Also encompassed by the present invention is a method of treating and/or preventing diabetes mellitus in a mammal comprising the step of administering to a mammal a therapeutically effective amount of a compound of the present invention.

Also encompassed by the present invention is a method of treating and/or preventing cardiovascular disease in a mammal comprising the step of administering to a mammal a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof.

Also encompassed by the present invention is a method of treating and/or preventing syndrome X in a mammal comprising the step of administering to the mammal a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof.

Also encompassed by the present invention is a method of treating and/or preventing disease or condition in a mammal selected from the group consisting of hyperglycemia, dyslipidemia, Type II diabetes, Type I diabetes, hypertriglyceridemia, syndrome X, insulin resistance, heart failure, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, hypertension, obesity, anorexia bulimia, anorexia nervosa, cardiovascular disease and other diseases where insulin resistance is a component, comprising the step of administering an effective amount of a compound of the present invention, and an effective amount of second therapeutic agent selected from the group consisting of insulin sensitizers, sulfonylureas, biguanides, meglitinides, thiazolidinediones, α-glucosidase inhibitors, insulin secretogogues, insulin, antihyperlipidemic agents, plasma HDL-raising agents, HMG-CoA reductase inhibitors, statins, acryl CoA:cholestrol acyltransferase inhibitors, antiobesity compounds, antihypercholesterolemic agents, fibrates, vitamins and aspirin.

Also encompassed by the present invention is use of a compound of the present invention and a pharmaceutically acceptable salt, solvate, hydrate or stereoisomer thereof, for the manufacture of a medicament for the treatment of a condition modulated by a PPAR.

The terms used to describe the present invention have the following meanings unless otherwise indicated.

The term "alkyl," unless otherwise indicated, refers to those alkyl groups of a designated number of carbon atoms of either a straight or branched saturated configuration. Examples of "alkyl" include, but are not limited to: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl and tert-butyl, pentyl, hexyl, isopentyl and the like. Alkyl as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "alkoxy" represents an alkyl group of indicated number of carbon atoms attached through an oxygen bridge, such as methoxy, ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy, pentoxy, and the like. Alkoxy as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "cycloalkyl" refers to a saturated or partially saturated carbocycle containing one or more rings of from 3 to 12 carbon atoms, more typically 3 to 8 carbon atoms. Examples of cycloalkyl includes, but are not limited to cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, and the like. Cycloalkyl as defined above may also includes a tricycle, such as adamantyl. Cycloalkyl as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "halo" refers to fluoro, chloro, bromo and iodo.

The term "haloalkyl" is a C_1-C_6 alkyl group, which is substituted with one or more halo atoms selected from F, Br, Cl and I. Examples of haloalkyl group are trifluoromethyl, CH_2CF_3 and the like.

The term "haloalkyloxy" represents a C_1-C_6 haloalkyl group attached through an oxygen bridge, such as OCF_3. The "haloalkyloxy" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "aryl" includes carbocyclic aromatic ring systems (e.g. phenyl), fused polycyclic aromatic ring systems (e.g. naphthyl and anthracenyl) and aromatic ring systems fused to carbocyclic non-aromatic ring systems (e.g., 1,2,3,4-

tetrahydronaphthyl). The "aryl" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The term "aryloxy" represents an aryl group attached through an oxygen bridge, such as phenoxy (-O-phenyl). The "aryloxy" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The "acyl" represent an "alkyl-C(=O)-" group. Preferred acyl group are those in which the alkyl group is lower alkyl, such C_1-C_4 alkyl.

The term "heteroaryl" group, as used herein, is an aromatic ring system having at least one heteroatom such as nitrogen, sulfur or oxygen and includes monocyclic, bicyclic or tricyclic aromatic ring of 5- to 14-carbon atoms containing one or more heteroatoms selected from O, N, or S. The heteroaryl as defined above also includes heteroaryl fused with another heteroaryl, aryl fused with heteroaryl or aryl fused with heterocyclyl as defined herein. The "heteroaryl" may also be optionally substituted with a designated number of substituents as set forth in the embodiment recited above. Examples of heteroaryl are, but are not limited to: furanyl, thienyl (also referred to as "thiophenyl"), thiazolyl, imidazolyl, indolyl, isoindolyl, isooxazolyl, oxazoyl, pyrazolyl, pyrrolyl, pyrazinyl, pyridyl, pyrimidyl, pyrimidinyl and purinyl, cinnolinyl, benzofuranyl, benzothienyl (or benzothiophenyl), benzotriazolyl, benzoxazolyl, quinoline, isoxazolyl, isoquinoline 1,4 benzodioxan, or 2,3-dihydrobenzofuranyl and the like.

The term "heterocyclyl" refers to a non-aromatic ring which contains one or more heteroatoms selected from O, N or S, which includes a monocyclic, bicyclic or tricyclic ring of 5- to 14-carbon atoms containing one or more heteroatoms selected from O, N or S. The "heterocyclyl" as defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above. Examples of heterocyclyl include, but are not limited to, morpholine, piperidine, piperazine, pyrrolidine, and thiomorpholine.

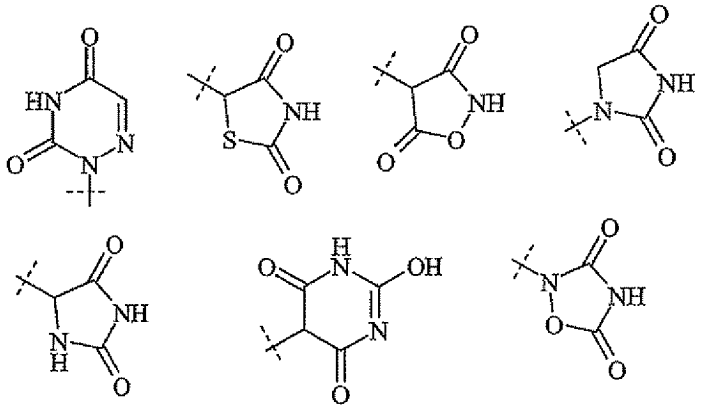
The term "carbocyclyl" (or carbocyclic ring) refers to a saturated or partially saturated carbocyclic ring. Examples of carbocyclyl are, but are not limited to, cyclopentyl, cyclohexyl, cyclopentenyl, cyclohexenyl and the like.

An "arylalkyl" as used herein is an aryl substituent that is linked to a compound by an alkyl group having from one to six carbon atoms. The "arylalkyl" as

defined above may be optionally substituted with a designated number of substituents as set forth in the embodiment recited above.

The "aminoalkyl" as used herein contains both a basic amino group (NH_2) and an alkyl group as defined above.

The term R^{6A} (or acid bioisosteres) as used herein includes, but are not limited to, carboxamide, sulfonamide, acylsulfonamide, tetrazole or the following moiety.



Carboxamide, sulfonamide, acylsulfonamide and tetrazole may be optionally substituted with one or more suitable substituents selected from haloalkyl, aryl, heteroaryl, and C_1-C_6 alkyl. The heteroalkyl, aryl, heteroaryl and alkyl may further optionally substituted with one or more substituents selected from the list provided for R^8. The examples of R^{6A} (or acid bioisosteres) are, but not limited to, hydroxamic acid, acyl cyanamide, tetrazoles, sulfinylazole, sulfonylazole, 3-hydroxyisoxazole, hydroxythiadiazole, sulphonate and acylsulfonamide.

The term "active ingredient" means the compounds generically described by Formula I as well as the salts, solvates and prodrugs of such compounds.

The term "pharmaceutically acceptable" means that the carrier, diluents, excipients and salt must be compatible with the other ingredients of the composition, and not deleterious to the recipient thereof. Pharmaceutical compositions of the present invention are prepared by procedures known in the art using well-known and readily available ingredients.

"Preventing" refers to reducing the likelihood that the recipient will incur or develop any of the pathological conditions described herein.

"Treating" refers to mediating a disease or condition, and preventing or mitigating its further progression or ameliorating the symptoms associated with the disease or condition.

"Pharmaceutically-effective amount" means that amount of a compound of the present invention, or of its salt, solvate, hydrate or prodrug thereof that will elicit the biological or medical response of a tissue, system or mammal. Such an amount can be administered prophylactically to a patient thought to be susceptible to development of a disease or condition. Such amount when administered prophylactically to a patient can also be effective to prevent or lessen the severity of the mediated condition. Such an amount is intended to include an amount, which is sufficient to modulate a PPAR receptor such as a PPARα, PPARγ, PPARδ or PPARγ/δ receptor to mediate a disease or condition. Conditions mediated by PPAR receptors include, for example, diabetes mellitus, cardiovascular disease, Syndrome X, obesity and gastrointestinal disease. Additional conditions associated with the modulation of a PPAR receptor include inflammation related conditions, which include, for example, IBD (inflammatory bowel disease), rheumatoid arthritis, psoriasis, Alzheimer's disease, Chrohn's disease and ischemia reprofusion injury (stroke and miocardial infarction).

A "mammal" is an individual animal that is a member of the taxonomic class mammalia. The class Mammalia includes humans, monkeys, chimpanzees, gorillas, cattle, swine, horses, sheep, dogs, cats, mice, rats and the like.

Administration to a human is most preferred. A human to whom the compounds and compositions of the present invention are administered has a disease or condition in which control blood glucose levels are not adequately controlled without medical intervention, but wherein there is endogenous insulin present in the human's blood. Non-insulin dependent diabetes mellitus (NIDDM) is a chronic disease or condition characterized by the presence of insulin in the blood, even at levels above normal, but resistance or lack of sensitivity to insulin action at the tissues.

Those skilled in the art will recognize that stereocenters exist in compound of the present invention. Accordingly, the present invention includes all possible stereoisomers and geometric isomers of the presently claimed compounds including racemic compounds and the optically active isomers.

The compounds of the present invention contain one or more chiral centers and exist in different optically active forms. When compounds of the present invention contain one chiral center, the compounds exist in two enantiomeric forms and the present invention includes both enantiomers and mixtures of enantiomers, such as racemic mixtures. Resolution of the final product, an intermediate or a starting material may be effected by any suitable method known in the art, for example by formation of diastereoisomeric salts which may be separated by crystallization; formation of diastereoisomeric derivatives or complexes which may be separated by crystallization and gas-liquid or liquid chromatography; selective reaction of one enantiomer with an enantiomer-specific reagent such as enzymatic esterification; and gas-liquid or liquid chromatography in a chiral environment such as on a chiral support, for example silica with a bound chiral ligand or in the presence of a chiral solvent. See also *Sterochemistry of Carbon Compounds* by E.L. Eliel (Mcgraw Hill, 1962) and *Tables of Resolving Agents* by S. H. Wilen. It will be appreciated that where the desired enantiomer is converted into another chemical entity by one of the separation procedures described above, a further step is required to liberate the desired enantiomeric form. Alternatively, specific enantiomers may be synthesized by asymmetric synthesis using optically active reagents, substrates, catalysts or solvents, or by converting one enantiomer into the other by asymmetric transformation.

When a compound of the present invention has more than one chiral substituents, it may exist in diastereoisomeric forms. The diastereoisomeric pairs may be separated by methods known to those skilled in the art, for example chromatography or crystallization and the individual enantiomers within each pair may be separated as described above. The present invention includes each diastereoisomer of compounds of formula I and mixtures thereof.

Certain compounds of the present invention may exist in different stable conformational forms, which may be separable. Torsional asymmetry due to restricted rotation about an asymmetric single bond, for example because of steric hindrance or ring strain, may permit separation of different conformers. The present invention includes each conformational isomer of compounds of formula I and mixtures thereof.

Certain compound of the present invention may exist in zwitterionic form, and the present invention includes each zwitterionic form of compounds of formula I and mixtures thereof.

Certain compounds of the present invention and their salts may exist in more than one crystal form. Polymorphs of compounds of formula I form part of the present invention and may be prepared by crystallization of a compound of formula I under different conditions, such as using different solvents or different solvent mixtures for recrystallization; crystallization at different temperatures; and various modes of cooling ranging from very fast to very slow cooling during crystallization. Polymorphs may also be obtained by heating or melting a compound of formula I followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or other available techniques.

Certain compounds of the present invention and their salts may exist in more than one crystal form, which includes each crystal form and mixtures thereof.

Certain compounds of the present invention and their salts may also exist in the form of solvates, for example hydrates, and thus the present invention includes each solvate and mixtures thereof.

"Pharmaceutically-acceptable salt" refers to salts of the compounds of formula I, which are substantially non-toxic to mammals. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a mineral, organic acid: an organic base or inorganic base. Such salts are known as base addition salts, respectively. It should be recognized that the particular counterion forming a part of any salt of the present invention is not of a critical nature so long as the salt as a whole is pharmaceutically acceptable and the counterion does not contribute undesired qualities to the salt as a whole.

By virtue of its acidic moiety, a compound of the present invention forms salts with pharmaceutically acceptable bases. Some examples of base addition salts include metal salts such as aluminum; alkali metal salts such as lithium, sodium or potassium; and alkaline earth metal salts such as calcium, magnesium, ammonium, or substituted ammonium salts. Examples of substituted ammonium salts include, for instance, those with lower alkylamines such as trimethylamine and triethylamine;

hydroxyalkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine; cycloalkylamines such as bicyclohexylamine or dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bisdehydro-abietylamine, glucamine, N-piperazine methylglucamine; bases of the pyridine type such as pyridine, collidine, quinine or quinoline; and salts of basic amino acids such as lysine and arginine.

Examples of inorganic bases include, without limitation, sodium hydroxide, potassium hydroxide, potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like.

Compounds of the present invention, which are substituted with a basic group, may exist as salts with pharmaceutically acceptable acids. The present invention includes such salts. Examples of such salts include hydrochlorides, hydrobromides, sulfates, methanesulfonates, nitrates, maleates, acetates, citrates, fumarates, tartrates [e.g. (+)-tartrates, (-)-tartrates or mixtures thereof including racemic mixtures], succinates, benzoates and salts with amino acids such as glutamic acid. These salts may be prepared by methods known to those skilled in the art.

Certain compounds of the present invention and their salts may also exist in the form of solvates, for example hydrates, and thus the present invention includes each solvate and mixtures thereof.

The compounds of present invention, which bind to and activate the PPARs, lower one or more of glucose, insulin, triglycerides, fatty acids and/or cholesterol, and are therefore useful for the treatment and/or prevention of hyperglycemia, dyslipidemia and in particular Type II diabetes as well as other diseases including syndrome X, Type I diabetes, hypertriglyceridemia, insulin resistance, diabetic dyslipidemia, hyperlipidemia, hypercholesteremia, heart failure, coagaulopathy, hypertension, and cardiovascular diseases, especially arteriosclerosis. In addition, these compounds are indicated to be useful for the regulation of appetite and food intake in subjects suffering from disorders such as obesity, anorexia bulimia and anorexia nervosa.

The compounds and compositions of the present invention are also useful to treat acute or transient disorders in insulin sensitivity, which sometimes occurs following a surgery, trauma, myocardial infarction and the like. The compounds and compositions of the present invention are also useful for lowering serum triglyceride levels. Elevated triglyceride level, whether caused by genetic predisposition or by a high

fat diet, is a risk factor for the development of heart disease, stroke, and circulatory system disorders and diseases. The physician of ordinary skill will know how to identify humans who can benefit from administration of the compounds and compositions of the present invention.

The present invention further provides a method for the treatment and/or prophylaxis of hyperglycemia in a human or non-human mammal which comprises administering an effective, non-toxic amount of a compound of formula I, or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof to a hyperglycemic human or non-human mammal in need thereof.

The compounds of the present invention are useful as therapeutic substances in preventing or treating Syndrome X, diabetes mellitus and related endocrine and cardiovascular disorders and diseases in human or non-human animals.

The present invention also relates to the use of a compound of formula I as described above for the manufacture of a medicament for treating a PPARγ or PPARδ mediated condition, separately or in combination.

A therapeutically effective amount of a compound of the present invention can be used for the preparation of a medicament useful for treating Syndrome X, diabetes, treating obesity, lowering tryglyceride levels, raising the plasma level of high density lipoprotein, and for treating, preventing or reducing the risk of developing arteriosclerosis, and for preventing or reducing the risk of having a first or subsequent atherosclerotic disease event in mammals, particularly in humans. In general, a therapeutically effective amount of a compound of formula I of the present invention typically reduces serum glucose levels, more specifically HbA1c, of a patient by about 0.7% or more; typically reduces serum triglyceride levels of a patient by about 20% or more; and increases serum HDL levels in a patient. Preferably, HDL levels can be increased by about 30% or more.

Additionally, an effective amount of a compound of the present invention and a therapeutically effective amount of one or more active agents selected from antihyperlipidemic agent, plasma HDL-raising agents, antihypercholesterolemic agents, fibrates, vitamins, aspirin, insulin secretogogues, insulin and the like can be used together for the preparation of a medicament useful for the above described treatments.

Advantageously, compositions containing the compound of the present invention or their salts may be provided in dosage unit form, preferably each dosage unit containing from about 1 to about 500 mg. It is understood that the amount of the compounds or compounds of the present invention that will be administered is determined by a physician considering of all the relevant circumstances.

Syndrome X includes pre-diabetic insulin resistance syndrome and the resulting complications thereof, insulin resistance, non-insulin dependent diabetes, dyslipidemia, hyperglycemia obesity, coagulopathy, hypertension and other complications associated with diabetes. The methods and treatments mentioned herein include the above and encompass the treatment and/or prophylaxis of any one of or any combination of the following: pre-diabetic insulin resistance syndrome, the resulting complications thereof, insulin resistance, Type II or non-insulin dependent diabetes, dyslipidemia, hyperglycemia, obesity and the complications associated with diabetes including cardiovascular disease, especially arteriosclerosis.

The compositions are formulated and administered in the same general manner as detailed herein. The compounds of the present invention may be used effectively alone or in combination with one or more additional active agents depending on the desired target therapy. Combination therapy includes administration of a single pharmaceutical dosage composition, which contains a compound of the present invention and one or more additional active agents, as well as administration of a compound of the present invention and each active agent in its own separate pharmaceutical dosage. For example, a compound of the present invention or thereof and an insulin secretogogue such as biguanides, meglitinides, thiazolidinediones, sulfonylureas, insulin or α-glucosidose inhibitors can be administered to the patient together in a single oral dosage composition such as a tablet or capsule, or each agent administered in separate oral dosages. Where separate dosages are used, a compound of the present invention and one or more additional active agents can be administered at essentially the same time, i.e., concurrently or at separately staggered times, i.e., sequentially; combination therapy is understood to include all these regimens.

An example of combination treatment or prevention of arteriosclerosis may involve administration of a compound of the present invention or salts thereof in combination with one or more of second active therapeutic agents: antihyperlipidemic

agents; plasma HDL-raising agents; antihypercholesterolemic agents, fibrates, vitamins, aspirin and the like. As noted above, the compounds of the present invention can be administered in combination with more than one additional active agent.

Another example of combination therapy can be seen in treating diabetes and related disorders wherein the compounds of the present invention or salts thereof can be effectively used in combination with second active therapeutic, such as sulfonylureas, biguanides, meglitinides, thiazolidinediones, α-glucosidase inhibitors, other insulin secretogogues, insulin as well as the active agents discussed above for treating arteriosclerosis.

The examples of second therapeutic agents are insulin sensitizers, PPARγ agonists, glitazones, troglitazone, pioglitazone, englitazone, MCC-555, BRL 49653, biguanides, metformin, phenformin, insulin, insulin minetics, sufonylureas, tolbutamide, glipizide, alpha-glucosidase inhibitors, acarbose, cholesterol lowering agent, HMG-CoA reductase inhibitors, lovastatin, simvastatin, pravastatin, fluvastatin, atrovastatin, rivastatin, other statins, sequestrates, cholestyramine, colestipol, dialkylaminoalkyl derivatives of a cross-linked dextran, nicotinyl alcohol, nicotinic acid: a nicotinic acid salt, PPARα agonists, fenofibric acid derivatives, gemfibrozil, clofibrate, fenofibrate, benzafibrate, inhibitors of cholesterol absorption, beta-sitosterol, acryl CoA:cholesterol acyltransferase inhibitors, melinamide, probucol, PPARδ agonists, antiobesity compounds, fenfluramine, dexfenfluramine, phentiramine, sulbitramine, orlistat, neuropeptide Y5 inhibitors, β_3 adrenergic receptor agonists, and ileal bile acid transporter inhibitors.

The compounds of the present invention and the pharmaceutically acceptable salts, solvates and hydrates thereof have valuable pharmacological properties and can be used in pharmaceutical compositions containing a therapeutically effective amount of a compound of the present invention, or pharmaceutically acceptable salts, esters or prodrugs thereof, in combination with one or more pharmaceutically acceptable excipients. Excipients are inert substances such as, without limitation carriers, diluents, fillers, flavoring agents, sweeteners, lubricants, solubilizers, suspending agents, wetting agents, binders, disintegrating agents, encapsulating material and other conventional adjuvants. Proper excipient is dependent upon the route of administration chosen.

Pharmaceutical compositions typically contain from about 1 to about 99 weight percent of the active ingredient, which is a compound of the present invention.

Preferably, the pharmaceutical formulation is in unit dosage form. A "unit dosage form" is a physically discrete unit containing a unit dose suitable for administration in human subjects or other mammals. For example, a unit dosage form can be a capsule or tablet, or a number of capsules or tablets. A "unit dose" is a predetermined quantity of the active compound of the present invention, calculated to produce the desired therapeutic effect, in association with one or more pharmaceutically acceptable excipients. The quantity of active ingredient in a unit dose may be varied or adjusted from about 0.1 to about 1000 milligrams or more according to the particular treatment involved.

The dosage regimen utilizing the compounds of the present invention is selected by one of ordinary skill in the medical or veterinary arts considering various factors, such as without limitation, the species, age, weight, sex, medical condition of the recipient, the severity of the condition to be treated, the route of administration, the level of metabolic and excretory function of the recipient, the dosage form employed, the particular compound and salt thereof employed, and the like.

Preferably, the compounds of the present invention are administered in a single daily dose, or the total daily dose may be administered in divided doses of two, three or more times per day. Where delivery is via transdermal forms, administration is continuous.

Suitable routes of administration of pharmaceutical compositions of the present invention include, for example, oral, eye drop, rectal, transmucosal, topical or intestinal administration; parenteral delivery (bolus or infusion), including intramuscular, subcutaneous, intramedullary injections, as well as intrathecal, direct intraven-tricular, intravenous, intraperitoneal, intranasal, or intraocular injections. The compounds of the present invention can also be administered in a targeted drug delivery system, such as in a liposome coated with endothelial cell-specific antibody.

For oral administration, the compounds of the present invention can be formulated readily by combining the active compounds with pharmaceutically acceptable carriers well known in the art. Such carriers enable the compounds of the present invention to be Formulated as tablets, pills, powders, sachets, granules, dragees, capsules,

liquids, elixirs, tinctures, gels, emulsions, syrups, slurries, suspensions and the like, for oral ingestion by a patient to be treated. Pharmaceutical preparations for oral use can be obtained by combining the active compound with a solid excipient, optionally grinding a resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores.

For oral administration in the form of a tablet or capsule, the active ingredient may be combined with an oral, non-toxic, pharmaceutically-acceptable carrier, such as, without limitation, lactose, starch, sucrose, glucose, methyl cellulose, calcium carbonate, calcium phosphate, calcium sulfate, sodium carbonate, mannitol, sorbitol, and the like; together with, optionally, disintegrating agents, such as, without limitation, cross-linked polyvinyl pyrrolidone, maize, starch, methyl cellulose, agar, bentonite, xanthan gum, alginic acid: or a salt thereof such as sodium alginate, and the like; and, optionally, binding agents, for example, without limitation, gelatin, acacia, natural sugars, beta-lactose, corn sweeteners, natural and synthetic gums, acacia, tragacanth, sodium alginate, carboxymethyl-cellulose, polyethylene glycol, waxes, and the like; and, optionally, lubricating agents, for example, without limitation, magnesium stearate, sodium stearate, stearic acid: sodium oleate, sodium benzoate, sodium acetate, sodium chloride, talc, and the like. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil.

Solid forms include powders, tablets and capsules. A solid carrier can be one or more substances, which may also act as flavoring agents, lubricants, solubilisers, suspending agents, binders, tablet disintegrating agents and encapsulating material.

In powders, the carrier is a finely divided solid, which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

Various other materials may be present as coatings or to modify the physical form of the dosage unit. For instance, tablets may be coated with shellac, sugar or both. A syrup or elixir may contain, in addition to the active ingredient, sucrose as a sweetening agent, methyl and propylparabens as preservatives, a dye and a flavoring such as cherry or orange flavor.

Sterile liquids include suspensions, emulsions, syrups, and elixirs. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable carrier, such as sterile water, sterile organic solvent, or a mixture of both sterile water and sterile organic solvent.

The active ingredient can also be dissolved in a suitable organic solvent, for example, aqueous propylene glycol. Other compositions can be made by dispersing the finely divided active ingredient in aqueous starch or sodium carboxymethyl cellulose solution or in a suitable oil.

Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for identification or to characterize different combinations of active compound doses.

Pharmaceutical preparations, which can be used orally, include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In addition, stabilizers may be added.

All formulations for oral administration should be in dosages suitable for such administration. Particularly suitable compositions for oral administration are unit dosage forms such as tablets and capsules.

For parental administration, the compounds of the present invention or salts thereof can be combined with sterile aqueous or organic media to form injectable solutions or suspensions. Formulations for injection may be presented in unit dosage form, such as in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions and sterile powders for the extemporaneous

preparation of sterile injectable solutions or dispersions. In all cases, the form must be sterile and must be fluid to the extent that each syringability exists. It must be stable under the conditions of manufacture and storage and must be preserved against any contamination. The carrier can be solvent or dispersion medium containing, for example, water, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiological saline buffer, ethanol, polyol (e.g. glycerol, propylene glycol and liquid polyethylene glycol), propylene glycol and liquid polyethylene glycol), suitable mixtures thereof, and vegetable oils. Under ordinary conditions of storage and use, these preparations contain a preservative to prevent the growth of microorganisms.

The injectable solutions prepared in this manner can then be administered intravenously, intraperitoneally, subcutaneously, or intramuscularly, with intramuscular administration being preferred in humans.

For transmucosal administration, penetrants appropriate to the barrier to be permeated are used in the formulation. Such penetrants are generally known in the art. The active compounds can also be administered intranasally as, for example, liquid drops or spray.

For buccal administration, the compositions may take the form of tablets or lozenges Formulated in a conventional manner.

For administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of a dry powder inhaler, or an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant, e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of pressurized aerosol the dosage unit may be determined by providing a valve to deliver a metered amount. Capsules and cartridges of gelatin for use in an inhaler or insufflator may be formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

Pharmaceutical compositions of the present invention can be manufactured in a manner that is itself known, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or lyophilizing processes.

In making the compositions of the present invention, the active ingredient will usually be admixed with a carrier, or diluted by a carrier, or enclosed within a carrier, which may be in the form of a capsule, sachet, paper or other container. When the carrier serves as a diluent, it may be a solid, lyophilized solid or paste, semi-solid, or liquid material which acts as a vehicle, or can be in the form of tablets, pills, powders, lozenges, elixirs, suspensions, emulsions, solutions, syrups, aerosols (as a solid or in a liquid medium), or ointment, containing for example up to 10% by weight of the active compound. The compounds of the present invention are preferably formulated prior to administration.

Binding and Cotransfection Studies

The in vitro potency of compounds in modulating PPARγ, PPARα and PPARδ receptors are determined by the procedures detailed below. DNA-dependent binding (ABCD binding) is carried out using Scintillation Proximity Assay (SPA) technology with PPAR receptors. Tritium-labeled PPARα and PPARγ agonists are used as radioligands for generating displacement curves and IC_{50} values with compounds of the present invention. Cotransfection assays are carried out in CV-1 cells. The reporter plasmid contains an acylCoA oxidase (AOX) PPRE and TK promoter upstream of the luciferase reporter cDNA. Appropriate PPARs and RXRα are constitutively expressed using plasmids containing the CMV promoter. Since for PPARα and PPARβ, interference by endogenous PPARγ in CV-1 cells is an issue, in order to eliminate such interference, a GAL4 chimeric system is used in which the DNA binding domain of the transfected PPAR is replaced by that of GAL4, and the GAL4 response element is utilized in place of the AOX PPRE. Receptor activation by compounds of the present invention is determined relative to PPARα agonist and PPARγ agonist reference molecules to obtain percent efficacies. EC50 values are determined by computer fit to a concentration-response curve. A typical range for concentration determination is from 1nM to 10μM. For binding or cotransfection studies with receptors other than PPARs, similar assays are carried out using appropriate ligands, receptors, reporter constructs and etc. for that particular receptor. In some cases, a single high concentration of agonist (10 μM) was used.

These studies are carried out to evaluate the ability of compounds of the present invention to bind to and/or activate various nuclear transcription factors, particularly huPPARα ("hu" indicates "human"), huPPARγ and huPPARδ. These studies provide in-vitro data concerning efficacy and selectivity of compounds of the present invention. Furthermore, binding and cotransfection data for compounds of the present invention are compared with corresponding data for reference compounds that act on either huPPARα or huPPARγ.

The typical range of concentration for binding is from 1nM to 10μM. The concentration of test compound required to effect 50% maximal activation of PPARα ($IC_{50}\alpha$) and PPARγ ($IC_{50}\gamma$) is determined. The compounds of the present invention, in general, have IC_{50} or EC_{50} in the range of about 1nM to about 1000 nM for PPAR alpha, gamma or delta.

Evaluation of Triglyceride and Cholesterol Level in HuapoAI Transgenic Mice

Five to six week old male mice, transgenic for human apoAI [C57Bl/6-tgn(apoa1)1rub, Jackson Laboratory, Bar Harbor, ME] are housed five per cage (10"x20"x8" with aspen chip bedding) with food (Purina 5001) and water available at all times. After an acclimation period of 2 weeks, animals are individually identified by ear notches, weighed and assigned to groups based on body weight. Beginning the following morning, mice are dosed daily by oral gavage for 7 days using a 20 gauge, 1½" curved disposable feeding needle. Treatments are test compounds (30 mg/kg), a positive control (fenofibrate, 100 mg/kg) or vehicle [1% carboxymethylcellulose (w/v)/ 0.25% Tween80 (w/v); 0.2 ml/mouse]. Prior to termination on day 7, mice are weighed and dosed. Three hours after dosing, animals are anesthetized by inhalation of isoflurane (2-4%) and blood obtained via cardiac puncture (0.7-1.0 ml). Whole blood is transferred to serum separator tubes (Vacutainer SST), chilled on ice and permitted to clot. Serum is obtained after centrifugation at 4°C and frozen until analysis for triglycerides, total cholesterol, compound levels and serum lipoprotein profile by fast protein liquid chromatography (FPLC) coupled to an inline detection system. After sacrifice by cervical dislocation, the liver, heart and epididymal fat pads are excised and weighed.

The animals dosed with vehicle have average triglycerides values of about 60 to 80 mg/dl, which are reduced by the positive control fenofibrate (33-58 mg/dl with a mean reduction of 37%). The animals dosed with vehicle have average total serum cholesterol values of about 140 to180 mg/dl, which are increased by fenofibrate (about 190 to 280 mg/dl with a mean elevation of 41%). When subject to FPLC analysis, pooled sera from vehicle-treated hu apoAI transgenic mice have a high-density lipoprotein cholesterol (HDLc) peak area, which ranges from 47v-sec to 62v-sec. Fenofibrate increases the amount of HDLc (68-96v-sec with a mean percent increase of 48%). Test compounds evaluated in terms of percent increase in the area under the curve. Representative compounds of the present invention are tested using the above methods or substantially similar methods.

Evaluation of Glucose Levels in db/db Mice

Five week old male diabetic (db/db) mice [C57BlKs/j-m +/+ Lepr(db), Jackson Laboratory, Bar Harbor, ME] or lean littermates (db+) are housed 6 per cage (10"x20"x8" with aspen chip bedding) with food (Purina 5015) and water available at all times. After an acclimation period of 2 weeks, animals are individually identified by ear notches, weighed and bled via the tail vein for determination of initial glucose levels. Blood is collected (100 µl) from unfasted animals by wrapping each mouse in a towel, cutting the tip of the tail with a scalpel, and milking blood from the tail into a heparinized capillary tube balanced on the edge of the bench. Sample is discharged into a heparinized microtainer with gel separator (VWR) and retained on ice. Plasma is obtained after centrifugation at 4°C and glucose is measured immediately. Remaining plasma is frozen until the completion of the experiment, and glucose and triglycerides are assayed in all samples. Animals are grouped based on initial glucose levels and body weights. Beginning the following morning, mice are dosed daily by oral gavage for 7 days using a 20 gauge, 1½" curved disposable feeding needle. Treatments are test compounds (30 mg/kg), a positive control agent (30 mg/kg) or vehicle [1% carboxymethylcellulose (w/v)/0.25% Tween80 (w/v); 0.3 ml/mouse]. On day 7, mice are weighed and bled (tail vein) for about 3 hours after dosing. Twenty-four hours after the 7th dose (i.e., day 8), animals are bled again (tail vein). Samples obtained from conscious animals on days 0, 7 and 8 are assayed for glucose. After 24 hour bleed, animals are weighed and dosed for